landfall by instantaneously changing the surface beneath the storm from wet to dry. Under this model, the timescale of decay again increases with temperature.

The researchers then sought a physical explanation for why warming causes slower decay. The primary energy source for a tropical cyclone is the evaporation of water from the surface beneath the eyewall[5] (the band of cloud that surrounds the eye of the storm), which is rapidly cut off at landfall. But residual moisture in the storm provides a smaller, temporary, secondary source of energy[6]. The levels of this residual moisture are expected to increase with temperature on the basis of the laws of thermodynamics for moist air.

The authors tested the hypothesis that increased levels of residual moisture could cause slower decay using a second set of modelling experiments in which, in addition to drying the surface to mimic landfall, they removed all residual moisture in the atmosphere. These storms all showed identical timescales of decay, despite their different temperatures. Thus, it is the increased residual store of atmospheric moisture at warmer temperatures that slows the weakening of the storm.

A key outstanding question is the exact degree to which the decay rate depends on temperature. Although the empirical and modelling results are in qualitative agreement, temperature had a smaller effect on decay rate in the simulations than was estimated empirically. This difference might be due to the small size of the historical data set or to confounding factors in it. For example, there have been changes in the spatial distribution of landfall locations over time, and hence differences in the surface properties felt by the storms on land, such as surface moisture and roughness.

In addition, it is unclear whether the long-term trends seen in the historical data set might be affected by ongoing changes in the technologies with which researchers observe storms or in methods for estimating maximum storm wind speed over land. Information about these uncertainties is not readily available publicly, but an in-depth investigation of estimation practices would be worthwhile.

Analysis of historical data along coastal regions in other parts of the world, along with simulations over a broader range of temperatures and climates, could help to further test the robustness of the authors' findings for predicting future changes in decay rates. The effects of residual storm moisture also warrant further investigation to clarify how this effect can slow decay after landfall.

Li and Chakraborty's work highlights a key component of risk models that has been largely overlooked so far. Slower storm decay after landfall in the future would directly result in increases in total damage, and this would be exacerbated by increases in peak wind speed and total rainfall, both of which are expected to occur in a warming climate[7]. The extent of damage occurring inland depends on both the rate of storm decay and the speed of storm motion at landfall. Hence, a slower decay could also lead to increases in damage farther inland, although changes in the speed of motion remain a point of contention[8,9]. Longer-lived storms might also increase the chances of interaction with the jet stream, which can sometimes produce hazardous weather that can extend much farther inland[10].

More generally, the current results indicate the need to broaden our thinking about how climate change affects tropical cyclones after landfall. We must take into account residual atmospheric effects from the adjacent ocean, landfall location and effects induced by the land surface itself[6]. Integrating this understanding into hurricane models should help to improve our predictions of the future risks posed by individual storms and over the long term.

Dan Chavas and **Jie Chen** are in the Department of Earth, Atmospheric and Planetary Sciences, Purdue University, West Lafayette, Indiana 47907, USA.
e-mails: drchavas@gmail.com; chen2340@purdue.edu

1. Kaplan, J. & DeMaria, M. *J. Appl. Meteorol.* **34**, 2499–2512 (1995).
2. Jing, R. & Lin, N. *J. Adv. Model. Earth Syst.* **12**, e2019MS00197 (2020).
3. Li, L. & Chakraborty, P. *Nature* **587**, 230–234 (2020).
4. Bakkensen, L. A. & Mendelsohn, R. O. in *Hurricane Risk* (eds Collins, J. & Walsh, K.) 179–197 (Springer, 2019).
5. Tang, B. & Emanuel, K. *Bull. Am. Meteorol. Soc.* **93**, 1901–1912 (2012).
6. Chen, J. & Chavas, D. R. *J. Atmos. Sci.* **77**, 2807–2834 (2020).
7. Knutson, T. *et al. Bull. Am. Meteorol. Soc.* **101**, E303–E322 (2020).
8. Kossin, J. P. *Nature* **558**, 104–107 (2018).
9. Moon, I.-J., Kim, S.-H. & Chan, J. C. L. *Nature* **570**, E3–E5 (2019).
10. Evans, C. *et al. Mon. Weather Rev.* **145**, 4317–4344 (2017).

Immunology

Caspase-8 protein cuts a brake on immune defences

Igor E. Brodsky

The enzyme caspase-8 can induce cell death or promote survival and the expression of inflammatory proteins. The discovery of a previously unknown caspase-8 target solves one mystery about immune-defence regulation. **See p.275**

Activation of the protein caspase-8 can have consequences that include triggering a type of cell death called apoptosis, preventing another type of cell death termed necroptosis, and promoting gene expression that leads to inflammation. How the activity of this single protein regulates these distinct functions is unclear. On page 275, Gitlin *et al.*[1] shed light on how caspase-8 drives pro-inflammatory responses in mammalian cells (Fig. 1).

Caspase-8 is a protease, an enzyme that cleaves its target proteins. It is a central regulator of the various possible outcomes of cell-signalling pathways leading from receptors of the Toll-like receptor (TLR) or the tumour-necrosis factor receptor (TNFR) superfamilies[2]. Such signalling cascades ultimately activate the transcription-factor proteins NF-κB and AP-1, which modulate the expression of hundreds to thousands of genes that mediate inflammatory and antimicrobial responses during the innate immune response — the earliest response to infection.

Among the best studied of these genes are those encoding cytokine proteins that promote inflammation, which include tumour-necrosis factor (TNF), IL-6, IL-1 and IL-12, as well as members of a subfamily of cytokines called chemokines. These factors collectively marshal immune defences against infection, but can be associated with severe disease if their expression is not properly controlled[3]. Indeed, anti-TNF therapies are used extensively in the treatment of inflammatory diseases, but such treatments can also blunt defence against infections.

One potential outcome of caspase-8 activation after TLR or TNFR signalling is apoptosis. However, NF-κB, in addition to inducing the expression of mediators of inflammation, induces expression of genes that encode 'survival factors', which prevent cells from undergoing apoptosis[4,5]. In most healthy cells, therefore, these TLR or TNFR signalling pathways induce inflammation but do not cause cell death. However, if this receptor-mediated signalling is accompanied by a blockade of NF-κB, which occurs during infection by certain microorganisms, this triggers apoptosis that depends on caspase-8 and the enzyme RIPK1.

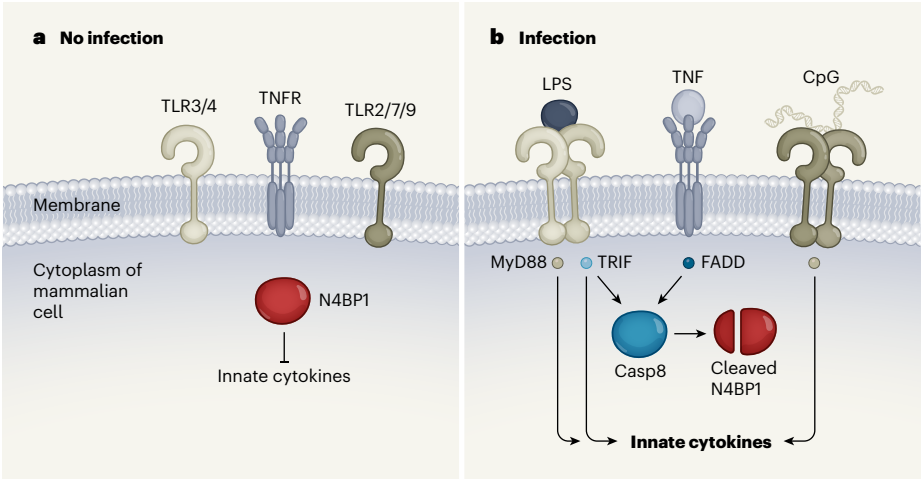

Figure 1 | A target of caspase-8 protein regulates production of defence molecules. a, Receptors from the Toll-like receptor (TLR) superfamily (such as TLR3 and TLR4 or TLR2, TLR7 and TLR9) and the tumour-necrosis factor receptor (TNFR) trigger defence responses during infection. Gitlin *et al.*[1] report that the protein N4BP1 can dampen the production of inflammatory molecules called cytokines, which are associated with the innate immune response. How N4BP1 causes this repression is unknown. **b**, In response to signs of bacterial infection that activate TLRs, such as the molecule lipopolysaccharide (LPS) or a DNA motif called CpG, the activated receptors assemble as protein pairs that signal to proteins such as MyD88 and TRIF (which only signals downstream of TLR3 and TLR4). This TLR activation boosts cytokine production. Gitlin and colleagues discovered that, when the enzyme caspase-8 (Casp8) is activated by the proteins TRIF or FADD (which acts downstream of TNFR activated by binding to the protein TNF), caspase-8 cleaves N4BP1. This boosts cytokine production by relieving the N4BP1-mediated repression of cytokine production. In contrast to TLR3/TLR4, which activate caspase-8 through TRIF, the TLRs that signal only through MyD88, such as TLR2, TLR7 and TLR9, do not directly activate caspase-8, but instead boost cytokine production through an indirect route that involves acting in synergy with TNFR-mediated caspase-8 activation.

This pathway provides a back-up host-defence mechanism to block the spread of pathogens that disrupt immune-system signalling[6–8].

Caspase-8 is also involved in the apoptosis of T cells of the immune system, which requires the activity of the proteins Fas and its ligand FasL. A deficiency in Fas or FasL results in a condition called autoimmune lymphoproliferative syndrome (ALPS), in which there is overproduction of immune cells[9]. Surprisingly, people with mutations that inactivate either caspase-8 or the protein FADD (which activates caspase-8 in response to signalling from TNFR) have an ALPS-like condition that is accompanied by immunodeficiency and higher-than-normal susceptibility to infections. This suggests that caspase-8 has additional functions in this context beyond regulating apoptosis[10,11].

Consistent with this idea, loss of caspase-8 inactivation in human T cells is associated with defects in the NF-κB-mediated gene expression that results from T-cell receptor stimulation[10,11]. However, because caspase-8 also has a key role in preventing necroptosis, which is an inflammatory form of caspase-independent cell death[12,13], it was initially unclear whether defects in gene expression in the setting of caspase-8 deficiency might be due to aberrant necroptosis[14].

A direct cell-intrinsic function of caspase-8 in regulating the expression of genes involved in innate immunity was subsequently revealed by the finding that deleting genes encoding the necroptosis-activating proteins RIPK3 or MLKL, in the setting of caspase-8 or FADD deficiency, reduced the activation of key inflammatory cytokine genes[15,16]. Caspase-8 deficiency has also been linked to reduced activation of the enzyme IKK, which is part of the pathway leading to NF-κB[8,17]. Nevertheless, how the single enzymatic activity of caspase-8 might promote apoptosis, yet also enable inflammatory gene expression, has remained mysterious. Now, Gitlin and colleagues have identified a direct target of caspase-8 whose inactivation by cleavage promotes the induction of a subset of the TLR-dependent inflammatory cytokines, providing a mechanistically satisfying explanation for how caspase-8 facilitates inflammatory gene expression.

"This work identifies a new regulator of a key signalling pathway of the innate immune system."

To identify caspase-8 cleavage targets in cells stimulated by TLR signalling, Gitlin *et al.* took advantage of the fact that caspases generate cleaved proteins that contain the amino-acid residue aspartate at their amino termini. Using an antibody that can recognize such aspartate residues, and mass spectrometry to identify the proteins, Gitlin and colleagues analysed extracts from mouse cells stimulated by exposure to lipopolysaccharide molecules. The authors compared the results for cells that did or did not receive a caspase inhibitor, and through this and other experiments identified the protein N4BP1 as a caspase-8 target that is cleaved in response to TLR or TNFR stimulation (Fig. 1).

N4BP1 was previously identified as a binding partner for the immune-signalling enzymes Nedd4 and Itch, and as a factor that restricts viral replication[18,19]. Gitlin *et al.* observed that N4BP1 was cleaved in a caspase-8-dependent manner in wild-type cells, or those lacking MLKL, following stimulation through the receptors TLR3, TLR4, TNFR or Fas. This cleavage occurred within one hour of stimulation. Among the TLRs tested, only TLR4 and TLR3 induced this rapid cleavage, which occurred after caspase-8 was activated by the TLR-associated protein TRIF.

The authors then confirmed that a deficiency in N4BP1 did not affect inflammatory cytokine expression in cells stimulated by lipopolysaccharides because such stimuli normally induce caspase-8-dependent inactivation of N4BP1. Crucially, Gitlin and colleagues report that the deletion of the gene encoding N4BP1 in cells also lacking caspase-8 reversed the defect in lipopolysaccharide-induced expression of several key cytokines, including TNF and IL-6. This observation provides direct evidence that caspase-8-dependent control of gene expression occurs, at least in part, through inactivation of N4BP1, and demonstrates that caspase-8 activity removes a brake on inflammatory gene expression.

TRIF-dependent TLRs activate caspase-8 directly[20] through interactions between TRIF and RIPK1. TLRs whose function instead depends on the protein MyD88 were not thought to directly activate caspase-8. Nevertheless, previous research[16] has indicated that MyD88-dependent TLRs also exploit caspase-8 for the optimal expression of inflammatory genes. Notably, Gitlin *et al.* report that the deletion of N4BP1 led to increased expression of several inflammatory cytokines and chemokines in response to stimulation of the MyD88-dependent TLRs, including TLR2, TLR7 and TLR9. This indicates that N4BP1 functions in suppressing inflammatory gene expression regulated by MyD88-dependent TLRs as well.

During infection, cells might encounter both pathogen-specific molecules (PAMPs) and other immune mediators, such as TNF, that can synergize with both TRIF- and MyD88-dependent TLRs to enhance inflammatory responses. Interestingly, Gitlin *et al.* observed that TNF stimulation enhanced gene expression downstream of MyD88-dependent TLRs, and that this enhancement required the cleavage of N4BP1 by caspase-8 that is

induced by TNF. The authors' study therefore highlights N4BP1's role as a broad negative regulator of TLR- and TNF-induced gene expression.

Mice engineered by the authors to lack N4BP1 survived embryonic development as usual and were fertile and essentially normal, but they developed a mild, age-dependent inflammation and immune dysregulation starting at around 14 weeks of age. This suggests that N4BP1 limits baseline inflammatory responses *in vivo*. Moreover, although blocking TNF signalling in wild-type mice increased their susceptibility to infection by the bacterium *Streptococcus pneumoniae*, most of the mice lacking N4BP1 survived this infection. This raises the possibility that the increased susceptibility to bacterial infections in people who receive anti-TNF treatment might be the result of a failure to inactivate N4BP1. Altogether, this work identifies a new regulator of a key signalling pathway of the innate immune system, and reveals a direct molecular target of caspase-8 in its role in controlling gene expression.

Exactly how N4BP1 suppresses cytokine gene expression is unclear. A deficiency in caspase-8 is associated with lower-than-usual levels of phosphorylation (addition of a phosphate group) of IKK[8,17]. However, Gitlin and colleagues found that deletion of N4BP1 does not restore wild-type levels of IKK phosphorylation in cells that lack both caspase-8 and MLKL, nor does it affect other aspects of the pathway leading to NF-κB activation, implying that N4BP1 probably regulates gene expression independently of NF-κB.

Notably, Gitlin *et al.* found that a substantial proportion (45%) of lipopolysaccharide-induced genes whose transcription was reduced in the absence of caspase-8 had higher levels of transcription if cells were deficient in both caspase-8 and N4BP1. Moreover, although caspase-8 deficiency blunts the expression of multiple cytokines, the genes most strongly affected by the presence of N4BP1 are those that encode the cytokines IL-6, TNF and G-CSF, which indicates that multiple caspase-8-dependent mechanisms probably integrate immune signalling to optimize inflammatory gene expression. Finally, how caspase-8 triggers apoptosis in some settings, yet mediates gene expression in non-apoptotic cells, also remains mysterious. Much remains to be learnt about this functionally versatile protein, and this study points the way to new avenues of discovery.

Igor E. Brodsky is in the Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine and Institute for Immunology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania 19104, USA.
e-mail: ibrodsky@vet.upenn.edu

1. Gitlin, A. D. *et al. Nature* **587**, 275–280 (2020).
2. Tummers, B. & Green, D. R. *Immunol. Rev.* **277**, 76–89 (2017).
3. van der Poll, T., van de Veerdonk, F. L., Scicluna, B. P. & Netea, M. G. *Nature Rev. Immunol.* **17**, 407–420 (2017).
4. Chen, C., Edelstein, L. C. & Gelinas, C. *Mol. Cell Biol.* **20**, 2687–2695 (2000).
5. Micheau, O., Lens, S., Gaide, O., Alevizopoulos, K. & Tschopp, J. *Mol. Cell Biol.* **21**, 5299–5305 (2001).
6. Peterson, L. W. *et al. J. Exp. Med.* **214**, 3171–3182 (2017).
7. Philip, N. H. *et al. Proc. Natl Acad. Sci. USA* **111**, 7385–7390 (2014).
8. Weng, D. *et al. Proc. Natl Acad. Sci. USA* **111**, 7391–7396 (2014).
9. Bidere, N., Su, H. C. & Lenardo, M. J. *Annu. Rev. Immunol.* **24**, 321–352 (2006).
10. Chun, H. J. *et al. Nature* **419**, 395–399 (2002).
11. Su, H. *et al. Science* **307**, 1465–1468 (2005).
12. Kaiser, W. J. *et al. Nature* **471**, 368–372 (2011).
13. Oberst, A. *et al. Nature* **471**, 363–367 (2011).
14. Ch'en, I. L., Tsau, J. S., Molkentin, J. D., Komatsu, M. & Hedrick, S. M. *J. Exp. Med.* **208**, 633–641 (2011).
15. Allam, R. *et al. EMBO Rep.* **15**, 982–990 (2014).
16. Philip, N. H. *et al. PLoS Pathog.* **12**, e1005910 (2016).
17. DeLaney, A. A. *et al. Proc. Natl Acad. Sci. USA* **116**, 11926–11935 (2019).
18. Oberst, A. *et al. Proc. Natl Acad. Sci. USA* **104**, 11280–11285 (2007).
19. Yamasoba, D. *et al. Nature Microbiol.* **4**, 1532–1544 (2019).
20. Kaiser, W. J. & Offermann, M. K. *J. Immunol.* **174**, 4942–4952 (2005).

This article was published online on 26 October 2020.

Nuclear physics

A deeper look at a cosmic nuclear reaction

Brian D. Fields

Experiments conducted deep beneath a mountain have provided the most precise measurements yet of a key nuclear reaction that occurred seconds after the Big Bang — refining our knowledge of the constituents of the Universe. **See p.210**

Cosmologists seek to infer the history of the Universe by using observations of today's cosmos to glean information about the exotic physics at play during its earliest moments. The epoch of Big Bang nucleosynthesis (BBN) represents a crucial frontier in this history. BBN is the process that produced the nuclei of the lightest elements, and started about one second after the Big Bang — the earliest time at which the known laws of physics left 'fossils' that can be probed experimentally[1]. On page 210, Mossa *et al.*[2] report measurements of nuclear reactions that sharpen our understanding of BBN, thereby allowing us to precisely measure the amount of 'ordinary' matter in the cosmos and potentially deepening our knowledge of the early Universe.

The Universe is expanding. We see this today in the systematic recession of galaxies, which spread to become ever more dilute with time. The present Universe is also cold, filled with thermal radiation known as the cosmic microwave background (CMB), which has a temperature of just under 3 kelvin. But the further back in time you go, the denser and hotter the Universe becomes, with cosmic particles having ever-higher energies and undergoing increasingly violent collisions. During the cosmic 'atomic age', when the Universe was 400,000 years old, it was so hot that atoms were unable to exist as bound objects, and ionized to form a plasma of free electrons and nuclei. And around one second after the Big Bang, the temperature was so high that atomic nuclei were unbound into their constituent neutrons and protons. This cosmic 'nuclear age' is the time of BBN.

When BBN began, the Universe was a hot soup of particles in which neutrons and protons were swarmed by photons and neutrinos[1]. The neutrons and protons combined as the Universe expanded and cooled, first forming a heavy isotope of hydrogen known as deuterium, whose nuclei consist of one proton and one neutron. The deuterium was then transformed by a series of reactions into helium-3 nuclei, and ultimately into helium-4 nuclei. After about three minutes, the Universe consisted of about 75% ordinary hydrogen nuclei and 25% helium-4, along with traces of deuterium, helium-3 and lithium-7. The Big Bang was thus the origin of the two most abundant elements in the Universe (hydrogen and helium), and made only light elements. Elements heavier than lithium-7 arose much later, during the deaths of the first stars.

To test theoretical models of BBN, cosmologists and astronomers observe the light elements in the Universe and infer their primordial abundances. Such observations[3] have confirmed that the primordial abundance of helium-4 was 25%. Measurements of deuterium[4] in the distant Universe offer further crucial information, because the ratio of the abundance of deuterium to that of hydrogen depends sensitively on the cosmic density of 'baryonic' matter — ordinary matter that consists of neutrons and protons, essentially